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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: David WALLACH et al.

Application No.: 10/035,408

Filed: January 4, 2002

For: MODULATORS OF REGULATORY PROTEINS

Art Unit: 1646

Examiner: Janet Andres

Washington, D.C.

Atty.'s Docket: WALLACH=17A

Date: July 22, 2005

Confirmation No. 3196

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Sir:

Transmitted herewith is an Appeal Brief in the above-identified application.

[XX] Fee for filing a brief in support of an appeal under 37 C.F.R. § 41.20(b)(2) $500.00

[ ] Small Entity Status: Applicant(s) claim small entity status. See 37 C.F.R. §1.27.

[ ] No additional fee is required.

[ ] The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA EQUALS	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
TOTAL	* 21	MINUS	** 33	0	x 25	$		x 50	$
INDEP.	* 1	MINUS	*** 3	0	x 100	$		x 200	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+ 180	$		+ 360	$
					ADDITIONAL FEE TOTAL	$	OR	TOTAL	$

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** If the "Highest Number Previously Paid for" IN THIS SPACE is less than 20, write "20" in this space.

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The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[ ] Conditional Petition for Extension of Time
If any extension of time for a response is required, applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity Response Filed Within		Other Than Small Entity Response Filed Within	
[ ] First -	$ 60.00	[ ] First -	$ 120.00
[ ] Second -	$ 225.00	[ ] Second -	$ 450.00
[ ] Third -	$ 510.00	[XX] Third -	$ 1020.00
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[ ] A check in the amount of $_____ is attached (check no.).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR §1.16 and all patent processing fees under 37 CFR §1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR §1.18.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

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IGOR METT and TANYA GONCHAROV

Application No. 10/035,408
Filed: January 4, 2002

MODULATORS OF REGULATORY PROTEINS

Examiner: J. Andres
Art Unit: 1646

APPEAL BRIEF

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REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited, an Israeli company of Ness-Ziona, Israel. Inter-Lab Limited is a subsidiary of InterPharm Laboratories Limited - an Israeli company of Ness-Ziona, Israel, which is a member of the Serono group of companies, whose parent company is Serono S.A., a holding company under which there are many subsidiaries worldwide.

RELATED APPEALS AND INTERFERENCES

Applicant is aware of a previous appeal involving issues which are similar to those involved in the present appeal. This is *Ex parte Wallach*, Appeal No. 1999-0197 in Application No. 08/054,970, the decision in which was mailed on November 21, 2001. Although the inventive entities are different (although there is an overlap of one inventor) and the inventions are different, the issues relate to a 35 U.S.C. § 112 rejection of screening claims. Thus, the decision may be considered to have a bearing on the Board's decision in the pending appeal. Out of an abundance of caution, the Board is being apprised of this appeal in accordance with Board Rule 41.37(c)(1)(ii).

STATUS OF CLAIMS

Claims 40, 41 and 50-56 are subject to the present appeal. Claims 34-36, 39 and 42-49 have been allowed and are not subject to the present appeal. Claims 1-33, 37 and 38 have been cancelled. The claims subject to the present appeal are presented in Part A of the Claims Appendix attached hereto. The claims that have been allowed are presented in Part B of the Claims Appendix.

STATUS OF AMENDMENTS

No amendment has been made subsequent to the final rejection of November 19, 2004, in this case.

SUMMARY OF CLAIMED SUBJECT MATTER

Claims 40, 50, 51, 52 and 56 all have identical language except that each is dependent from a different one of the claims that have already been allowed by the examiner. Similarly, claims 41, 53, 54 and 55 have identical language, but each are dependent from a different claim i.e., claims 40, 50, 51 and 52, respectively. Thus, to summarize the subject matter defined in each of the "independent claims involved in the appeal" as is required by Board Rule 41.37(c)(1)(v), one must first provide a concise explanation of the subject matter of the allowed independent claims from which the appealed claims depend.

Claim 34 is an allowed claim directed to a method for isolating and identifying polypeptides capable of binding to the death domain motif of a regulatory protein containing a death domain, which regulatory protein is either NGF-R, MORT-1 or ankyrin 1. The method includes the steps of assaying polypeptides to be tested for binding to the death domain motif of one of those regulatory proteins and then isolating and identifying any polypeptide that binds to such motif.

NGF-R, MORT-1 and ankyrin 1 are regulatory proteins that exert their effects by intracellular signaling processes which are mediated by regulatory elements (domains or motifs) contained within the intracellular domains of these proteins. See page 1, lines 11-14 of the present specification. The present invention is based on the discovery of a "death domain" motif present in a wide range of proteins, including

NGF-R, MORT-1 and ankyrin 1. See page 1, lines 17-22. It is expected that if polypeptides can be found capable of binding to or interacting with the "death domain" motifs of the "death domain" motif-containing proteins, then it will be possible to modulate the activity of those proteins. See page 16, lines 13-17. It is also desirable to isolate and characterize additional proteins or factors which may, for example, be involved further downstream in the signaling process and/or to isolate and identify other receptors further upstream in the signaling process to which these "death domain" motif-binding proteins bind, and hence, in whose function they are also involved. See page 17, lines 5-12. The screening method of claim 34 allows the isolation and identification of such polypeptides.

Claim 39, from which rejected claim 50 depends specifies that in the method of claim 34, the regulatory protein is NGF-R.

Claim 42, from which rejected claim 51 depends specifies that in the method of claim 34, the regulatory protein is MORT-1.

Claim 43, from which rejected claim 52 depends specifies that in the method of claim 34, the regulatory protein is ankyrin 1.

Claim 36, from which rejected claim 56 depends is a method of claim 34, but specifies that the assaying step involves applying the yeast two-hybrid procedure and the isolating and identifying step involves isolating the

positively transformed cells followed by extraction of the hybrid vector to obtain a sequence containing a protein, which binds to the death domain motif.

Dependent claims 40, 50, 51, 52 and 56, which all have identical language, modify the methods from which they depend by specifying that they are for isolating, identifying and producing the polypeptides capable of binding to a death domain motif and by further including the step of producing any polypeptide identified in the isolating and identifying step. This language is supported for example at page 60, lines 3-11 of the specification (paragraph [0107]), which states:

> The new proteins and peptides of the invention once isolated, identified and characterized by any of the standard screening procedures, for example, the yeast two-hybrid method, affinity chromatography, and any other well known method known in the art, may then be produced by any standard recombinant DNA procedure (see for example, Sambrook, et al., 1989) in which suitable eukaryotic or prokaryotic host cells are transformed by appropriate eukaryotic or prokaryotic vectors containing the sequences encoding for the proteins.

Claims 41, 53, 54 and 55, all of which have identical language, are dependent from claims 40, 50, 51 and 52, respectively, and specify that the producing step comprises producing the polypeptide by recombinant DNA procedure in which a eukaryotic or prokaryotic host cell is transformed by a eukaryotic or prokaryotic vector containing the sequence of said polypeptide. This language is also

supported by the same language of the specification quoted above.

None of the claims involved in the present appeal involve means plus function or step plus function language. The method claims recite acts, not functions, and therefore do not fall within the provisions of 35 U.S.C. § 112, paragraph 6. See *Seal-Flex Inc. v. Athletic Track and Court Construction,* 172 F.3d 836, 847-851, 50 U.S.P.Q.2d 1225, 1232-1235 (Fed. Cir. 1999), J. Rader, concurring opinion. See also *Masco Corp. v. U.S.*, 303 F.3d 1316, 1327, 64 U.S.P.Q.2d 1182, 1189 (Fed. Cir. 2002).

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 40, 41 and 50-56 have been rejected under 35 U.S.C. § 112, first paragraph as lacking written description. The examiner states that the claims encompass methods of producing proteins identified by a screening process, but in order to make such proteins, they must first be identified. The examiner states that, while methods for identification are set forth, no proteins are identified, other than the death domain containing proteins themselves, which appear to be able to associate with each other. The examiner states that one of skill in the relevant art would not conclude that Applicant was in possession of the genus of death domain binding proteins. The examiner states that there is no indication that the methods were actually implemented to identify any binding proteins, and that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, regardless of the complexity or simplicity of the methods of identification and production. Thus, the examiner states that, since Applicant is not in possession of the genus of death domain proteins, Applicant is not in possession of methods of producing them.

In the final rejection of November 19, 2004, the examiner stated, in response to Applicant's arguments:

> Methods of producing proteins are known and, as Applicant states, once a protein is isolated and identified the method of producing more of it is in the possession of the inventor. However, until the protein is isolated neither it nor the method of producing more of it are in

> possession of the inventor. The inventor would be possession of the product once it is found. However, the inventor is clearly not in possession of what has yet to be found and thus cannot produce more of it.

Claims 40, 41 and 50-56 have also been rejected under 35 U.S.C. § 112, first paragraph as lacking enablement commensurate in scope with the claims. The examiner states that the specification, while being enabling for methods of producing NGF-R, MORT-1 and ankyrin 1, does not reasonably provide enablement for producing death domain binding proteins as broadly claimed. The examiner again states that Applicant is not in possession of the proteins identified by the screening method, and as there are no working examples, it is not possible to produce such proteins. The examiner states that an assay for finding a product is not equivalent to a positive recitation of how to make a product, regardless of the ease of screening, and therefore would require undue experimentation to produce the proteins as claimed.

In the final rejection of November 19, 2004, in response to Applicant's arguments, the examiner stated:

> One of skill in the art might well be able to screen compounds. However, the nature of the compounds that will be identified by this method is not known. One cannot make something that has not been described. As Applicant states, it is a trivial matter to produce a protein once it has been identified. However, it is not a trivial matter to produce a protein that has not been identified. While Applicant is not claiming unidentified proteins, Applicant is claiming the means for making them. The production of any

identified protein would be enabled; however, one cannot produce what one has not identified.

ARGUMENT

Claims 40, 41 And 50-56 Are Described In The Specification In Such A Way As To Reasonably Convey That The Inventors Had Possession Of The Claimed Invention

All of the rejected claims are process claims generally comprising three steps. The first step is to assay polypeptides to be tested for binding to the death domain motif of a regulatory protein. The second step involves isolating and identifying "any polypeptide that binds to said motif." The third step is to produce "any polypeptide identified in said isolating and identifying step." Thus, the isolating and identifying step does not require that a polypeptide be found. Similarly, the producing step only requires a polypeptide to be produced if it has been identified in the isolating and identifying step. It may be that the assaying step will not find any molecules that bind to the target peptide. If so, then the isolating and identifying step and the subsequent producing step would not be performed. That situation does not mean that claim 37 as a whole fails to comply with the written description requirement.

The producing step only takes place after a polypeptide has been isolated and identified (if any such polypeptide is present in the material to be tested). The examiner does not deny that the claimed steps of assaying

polypeptides and isolating and identifying polypeptides that bind to the death domain motif would identify any target-binding molecule if it is present in the material being screened. The examiner has conceded that methods of producing proteins are known and that once a protein is isolated and identified, the method of producing more of it is in the possession of the inventor. The examiner further concedes at the top of page 3 of the final rejection of November 19, 2004:

> The inventor would be in possession of the product once it is found.

As the process includes finding the product as the initial steps, and as the examiner concedes that the inventor would be in possession of the product once it is found and that once a protein is isolated and identified the method of producing more of it is in the possession of the inventor, it must be concluded that the process of claim 40 is in the possession of the inventor and thus in full compliance with the written description requirement of 35 U.S.C. § 112.

The examiner's entire point appears to be that the inventor is not in possession of what has yet to be found and thus cannot produce more of it. However, the claims do not require that anyone produce more of anything that has not yet been found. The process involves the step of finding. The third step of producing <u>any</u> polypeptide identified in the

isolating and identifying step makes clear that such step need only take place if a product is found.

A case involving a similar issue has been decided by the Board of Patent Appeals and Interferences on November 21, 2001, Appeal No. 1999-0197, Application No. 08/054,970. This is a case arising from an invention out of the laboratory of the same Prof. David Wallach involved in the present appeal. A copy of this decision, *Ex parte David Wallach and Cord Brakebusch,* is attached hereto for the Board's consideration. While this decision was indicated as not being binding precedent of the Board, the manner of analysis should still be of interest to the present Board.

For all of these reasons, reversal of the examiner and withdrawal of the 35 U.S.C. § 112, first paragraph written description rejection are respectfully urged.

Claims 40, 41 and 50-56 Are Supported By An Enabling Disclosure Commensurate In Scope With The Claims

The examiner's reasoning in the enablement part of the present appeal is very closely linked to the written description reasoning discussed above. The examiner states that one cannot make something that has not been described. The examiner concedes at page 3 of the final rejection of November 19, 2004, that "it is a trivial matter to produce a protein once it has been identified." The examiner goes on to state, however, that it is not a trivial matter to produce a protein that has not been identified. What the examiner apparently fails to appreciate is that the claims do not encompass the production of a protein that has not been identified. The present claims only encompass the production of proteins that have been identified. The use of the term "producing any polypeptide identified in said isolating and identifying step" in claim 40 makes this clear.

As stated by a prior Board in the *Ex parte Wallach* decision, which is attached hereto, at page 8:

> [T]he examiner has lost sight of the fact that step b) of claim 37 only requires a screening step to identify any molecules which bind to the target peptide. Step c) only requires further screening if any molecules are identified in step b). It may be that the materials screened in screening step b) of claim 37 will not

> contain the specified molecules which bind to the target peptide. If so, then step c) would not be performed. That situation does not mean that claim 37 as whole is non-enabled. The examiner has not explained why the claimed screening methods would not identify the defined molecules if they are present in the material being screened.
>
> By way of analogy, let us consider a claim directed to separating iron scrap from a waste stream by use of magnets. The fact that the waste streams processed according to that method may never contain iron scrap does not mean that the method is non-enabled. [Emphasis original.]

By the same reasoning, claims 40, 41 and 50-56 as a whole are enabled. The examiner concedes that the screening methods would identify the defined molecules and then, once identified, it is a trivial matter to produce them. As the claims do not require that any protein be produced that has not been identified, the conclusion must be reached that the full scope of the claims are supported by an enabling disclosure.

Accordingly, reversal of the examiner and withdrawal of the 35 U.S.C. § 112, first paragraph enabling rejection of claims 40, 41 and 50-56 is respectfully urged.

CONCLUSION

The claims as submitted are believed to fully set forth the inventive concept of the present invention and to fully comply with the written description and enablement requirements of the first paragraph of 35 U.S.C. § 112. Accordingly, reversal of the examiner and allowance of claims 40, 41 and 50-56 are earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

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CLAIMS APPENDIX

Part A

This listing of claims includes all of the claims involved in the appeal.

Listing of Claims:

40. A method in accordance with claim 34 for isolating, identifying and producing said polypeptides capable of binding to a death domain motif, further including the step of producing any polypeptide identified in said isolating and identifying step.

41. A method in accordance with claim 40, wherein said producing step comprises producing said polypeptide by recombinant DNA procedure in which a eukaryotic or prokaryotic host cell is transformed by a eukaryotic or prokaryotic vector containing the sequence of said polypeptide.

50. A method in accordance with claim 39 for isolating, identifying and producing said polypeptides capable of binding to a death domain motif, further including the step of producing any polypeptide identified in said isolating and identifying step.

51. A method in accordance with claim 42 for isolating, identifying and producing said polypeptides capable

of binding to a death domain motif, further including the step of producing any polypeptide identified in said isolating and identifying step.

52. A method in accordance with claim 43 for isolating, identifying and producing said polypeptides capable of binding to a death domain motif, further including the step of producing any polypeptide identified in said isolating and identifying step.

53. A method in accordance with claim 50, wherein said producing step comprises producing said polypeptide by recombinant DNA procedure in which a eukaryotic or prokaryotic host cell is transformed by a eukaryotic or prokaryotic vector containing the sequence of said polypeptide.

54. A method in accordance with claim 51, wherein said producing step comprises producing said polypeptide by recombinant DNA procedure in which a eukaryotic or prokaryotic host cell is transformed by a eukaryotic or prokaryotic vector containing the sequence of said polypeptide.

55. A method in accordance with claim 52, wherein said producing step comprises producing said polypeptide by recombinant DNA procedure in which a eukaryotic or prokaryotic host cell is transformed by a eukaryotic or prokaryotic vector containing the sequence of said polypeptide.

56. A method in accordance with claim 36 for isolating, identifying and producing said polypeptides capable of binding to a death domain motif, further including the step of producing any polypeptide identified in said isolating and identifying step.

Part B

This listing of claims includes all of the claims which were allowed and are not involved in the appeal.

Listing of Claims:

34. A method for isolating and identifying polypeptides capable of binding to the death domain motif of a regulatory protein containing a death domain, said regulatory protein being NGF-R, MORT-1 or ankyrin 1, comprising:

assaying polypeptides to be tested, for binding to the death domain motif of a said regulatory protein; and

isolating and identifying any polypeptide that binds to said motif.

35. A method in accordance with claim 34, wherein said assaying step comprises applying the procedure of affinity chromatography in which said death domain motif is attached to an affinity chromatography matrix, and bringing said attached motif into contact with a cell extract; and wherein said isolating and identifying step comprises eluting, isolating and analyzing any polypeptides from the cell extract which bind to said attached motif.

36. A method in accordance with clam 34, wherein said assaying step comprises applying the yeast two-hybrid

procedure in which a sequence encoding the said death domain motif of a said regulatory protein is carried by one hybrid vector and a sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells; and wherein said isolating and identifying step comprises isolating the positive transformed cells, followed by extraction of said second hybrid vector to obtain a sequence encoding a protein which binds to said death domain motif.

39. A method in accordance with claim 34, wherein said regulatory protein is NGF-R.

42. A method in accordance with claim 34, wherein said regulatory protein is MORT-1.

43. A method in accordance with claim 34, wherein said regulatory protein is ankyrin 1.

44. A method in accordance with claim 39, wherein said assaying step comprises applying the procedure of affinity chromatography in which said death domain motif is attached to an affinity chromatography matrix, and bringing said attached motif into contact with a cell extract; and wherein said isolating and identifying step comprises eluting, isolating and analyzing any polypeptides from the cell extract which bind to said attached motif.

45. A method in accordance with claim 42, wherein said assaying step comprises applying the procedure of affinity chromatography in which said death domain motif is attached to an affinity chromatography matrix, and bringing said attached motif into contact with a cell extract; and wherein said isolating and identifying step comprises eluting, isolating and analyzing any polypeptides from the cell extract which bind to said attached motif.

46. A method in accordance with claim 43, wherein said assaying step comprises applying the procedure of affinity chromatography in which said death domain motif is attached to an affinity chromatography matrix, and bringing said attached motif into contact with a cell extract; and wherein said isolating and identifying step comprises eluting, isolating and analyzing any polypeptides from the cell extract which bind to said attached motif.

47. A method in accordance with clam 39, wherein said assaying step comprises applying the yeast two-hybrid procedure in which a sequence encoding the said death domain motif of a said regulatory protein is carried by one hybrid vector and a sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells; and wherein said isolating and identifying step comprises isolating the positive transformed cells, followed by extraction of said second

hybrid vector to obtain a sequence encoding a protein which binds to said death domain motif.

48. A method in accordance with clam 42, wherein said assaying step comprises applying the yeast two-hybrid procedure in which a sequence encoding the said death domain motif of a said regulatory protein is carried by one hybrid vector and a sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells; and wherein said isolating and identifying step comprises isolating the positive transformed cells, followed by extraction of said second hybrid vector to obtain a sequence encoding a protein which binds to said death domain motif.

49. A method in accordance with clam 43, wherein said assaying step comprises applying the yeast two-hybrid procedure in which a sequence encoding the said death domain motif of a said regulatory protein is carried by one hybrid vector and a sequence from a cDNA or genomic DNA library is carried by the second hybrid vector, the vectors then being used to transform yeast host cells; and wherein said isolating and identifying step comprises isolating the positive transformed cells, followed by extraction of said second hybrid vector to obtain a sequence encoding a protein which binds to said death domain motif.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

The Ex parte Wallach decision of November 21, 2001, in Appeal No. 1999-0197, follows this page.

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 32

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DAVID WALLACH and
CORD BRAKEBUSCH

Appeal No. 1999-0197
Application No. 08/054,970

HEARD: May 24, 2001

Before WILLIAM F. SMITH, SCHEINER, and MILLS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 34 through 38, 40, 42 through 44, 47 through 52, 54, 56, 57, and 60. Claims 39, 41, 45, 46, 49, 53, 55, 58, and 59 are pending but have been withdrawn from consideration by the examiner. Claims 34, 37, 42, 43, 44, and 60 are representative of the subject matter on appeal and read as follows:

34. A method of inhibiting signal transduction in tumor necrosis factor receptors (TNF-Rs), comprising:

identifying a molecule which binds to the portion of TNF-R which includes Ser197 or the amino acids 405 to 415 of human p55-TNF-R (SEQ ID NO:2) or the corresponding amino acids of the human p75-TNF-R, and thereby causes the signal transduction of said receptor to be inhibited; and

bringing said molecule into contact with said portion of TNF-R.

37. A method for identifying molecules which interact with TNF-R to modulate signal transduction by the TNF-R, comprising:

a) preparing a target peptide which includes amino acids 405-415 of human p55-TNF-R (SEQ ID NO:2) or the corresponding amino acids of human -75-TNF-R;

b) screening peptide libraries and/or broth of biological matter with said target peptide and identifying any molecules which bind to said target peptide; and

c) screening any molecules identified in step b) for their ability to modulate signal transduction of TNF-R and identifying any molecule which tests positive for such signal transduction modulation.

42. A method of inhibiting signal transduction in tumor necrosis factor receptors (TNS-Rs), comprising:

identifying a molecule which reacts with TNF-R to modulate signal transduction by the TNF-R, by means of a process in accordance with claim 37; and

bringing said molecule into contact with the portion of TNF-R which includes amino acids of human p75-TNF-R.

43. A method in accordance with claim 37, for identifying a molecule which interacts with TNF-R to inhibit signal transduction by the TNF-R, wherein said step c) comprises screening any molecules identified in step b) for their ability to inhibit signal transduction of TNF-R and identifying any molecule which tests positive for such signal transduction inhibition.

44. A method for preventing or treating a disease caused by tumor necrosis factor, comprising administering a molecule identifiable by the process of claim 43 in a manner by which said molecule can come into contact with the portion of the p55-TNF-R (SEQ ID NO:2) which includes Ser197 or amino acids 405-415, or the corresponding amino acids of human p75-TNF-R, in an amount effective to prevent or treat said disease.

60. A method for modulating the cleavage of the soluble form of TNF-R from TNF-R, comprising:

obtaining an antibody that binds to the human p55-TNF-R in the region of amino acids 170-174, 175-179 or 170-179 of human p55-TNF-R (SEQ ID NO:2) in a manner such that cleavage of the soluble form of TNF-R from the TNF-R is inhibited; and

bringing said antibody into contact with the portion of said TNF-R to which said antibody is specific.

The examiner does not rely upon prior art in rejecting the claims in the Examiner's Answer.

Claims 34 through 38, 40, 42 through 44, 47 through 52, 54, 56, 57, and 60 stand rejected under 35 U.S.C. § 112, first paragraph (enablement). We reverse and raise other issues for the examiner and appellants to consider.

Background

The claimed invention involves tumor necrosis factor receptors. As explained in the second full paragraph of page 1 of the specification:

> TNF, a pro-inflammatory cytokine produced primarily by macrophages, contributes to the defense of the host against pathogens as well as to various detrimental manifestations of inflammation through a variety of different effects on cell function (Old, 1990; Beutler and Cerami, 1989). These effects are initiated by the binding of TNF to specific, high affinity cell surface receptors (TNF-Rs), expressed on most kinds of cells (Baglioni et al., 1985; Beutler et al., 1985; Kull et al., 1985; Tsujimoto et

> al., 1985; Aggarwal et al., 1985; Israel et al., 1986). The receptors provide the intracellular signals for cell response to TNF (Englemann et al., 1990a). Two molecular species of the TNF-Rs, the p55 and the p75 TNF-R, expressed differentially in different types of cells, have been identified (Engelmann et al., 1990b; Brockhaus et al., 1990).

Appellants also explain on page 2 of the specification that:

> The main mediator for the cytotoxic effect of the TNF on fibroblastoid and epithelial cells is the p55 TNF-R, which also is the prevalent TNF-R type on these cell lines. Blocking this receptor species abolishes the cytocidal effect of TNF, while inducing aggregation of the receptor molecules can mimic the cytocidal effect of the TNF.
>
> The soluble form of this receptor, as well as the soluble form of the other (p75) TNF-R, have been shown to have inhibitory effects on TNF function. Evidence was presented that these soluble forms are derived proteolitically from the cell surface forms, (Nophar et al., 1990; Porteu and Nathan, 1990; Porteu et al., 1991).

The claimed invention is summarized at page 3 of the specification as follows:

> The present invention provides a method of modulating signal transduction and/or cleavage in tumor necrosis factor receptors (TNF-Rs) comprising interfering with one or more amino acids in the sequence of a TNF-R or with an effector protein interacting with the TNF-R.
>
> This interference influences the normal functioning of the TNF-Rs or influences an effector protein interacting therewith, and thereby modulates signal transduction by causing partial or total inhibition thereof, or influences shedding, i.e. abolishes cleavage of the soluble form of the receptor.
>
> The present invention further provides peptides or other molecules which interact either with the receptor itself, i.e. interact with one or more amino acids in the receptor sequence, or interact with the effector proteins, and thus modulate the normal functioning of the TNF-Rs. The above molecules also include antibodies or fragments thereof.

Appellants have found the role certain amino acids of human p55 TNF-R have in determining how the receptor functions. For example, appellants have found that transfectants expressing mutant receptors with deletion of the intercellular amino acids 405-426 were not responsive to antibodies against the human p55 TNF-R[1] (specification, page 6). Appellants state at page 7 of the specification that mutant receptors having amino acids 415-426 deleted confer to the transfected cells high responsiveness to cytocidal antibodies against the human p55 TNF-R. Appellants go on to say in the third and fourth paragraph on page 7 of the specification that:

> In a third mutant, a single serine residue (amino acid 197) in the transmembrane domain was exchanged by site directed mutagenesis against alanine, an amino acid said to be compatible with all known secondary structures of amino acid sequences. Functional analysis of cells transfected with this receptor mutant revealed a significant impairment in these receptors to trigger cell death in response to mimetic antibodies against the human p55 TNF-R. Yet this functional disruption was not complete and a small cytocidal effect could still be observed.
>
> Yet, other mutants, in which either amino acids 170-174, 175-179 or both, i.e., amino acids 170-179 were deleted, abolished shedding of the soluble extracellular forms of the receptor. This finding demonstrates that the region of amino acids 170-179 or part thereof, of the receptor, which lies just outside the transmembrane domain, must be intact in order to allow formation of the soluble TNF receptors. Therefore, any interference with this region, or the effector protein interacting therewith, will abolish shedding. The effector protein, in this case, is believed to be a proteolytic enzyme.

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[1] Appellants explain at page 6 of the specification that monoclonal antibodies against the human p55 TNF-R mimic TNF action.

For the purposes of considering the issues raised in this appeal, we believe the claims should be considered in two groups which we will denominate the use claims and the screening claims. Claims 34 through 36, 42, 44, 47, 48-50, 56, and 60 are the use claims. Claims 37, 38, 40, 43, 51, 52, and 54 are the screening claims. As can be seen, claim 37 is directed to a method for identifying molecules which interact with TNF-R to modulate signal transduction. The method comprises three steps: (1) preparing a specified target peptide, (2) screening peptide libraries and/or broth of biological matter with the target peptide and identifying any molecules which bind to the target peptide and (3) screening any molecules identified in the second step for their ability to modulate signal transduction of TNF-R to identify any molecule which tests positive for such signal transduction modulation. As can be seen, claim 37 does not require that any molecule be actually identified.

The use claims however do require the presence and use of a molecule which interacts with a specified portion of TNF-R. For example, claim 34 requires identification of a specific molecule and bringing that molecule into contact with a specified portion of TNF-R.

Discussion

We start our analysis with the proposition that the examiner bears the initial burden of providing reasons why the supporting disclosure does not enable a claim. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). In reviewing the examiner's statement of the rejection on pages 3-5 of the Answer, we find the examiner

is concerned that the specification does not set forth "one example of an agent that binds to the TNF-R at any set of amino acids or those amino acids set forth in Claims [sic] or its effector protein." The examiner also states at page 4 of the Answer that "it is not predictable what the agent is that will stabilize the TNF-R or will bind an effector protein to TNF-R, to blunt its signal transduction because there is not guidance in the specification as to what the characteristics of this (these) agent is." The examiner also questions the identity of the "effector protein" which forms part of the present invention. The examiner concludes at page 5 of the Answer that "it would require undue experimentation for one of ordinary skill in the art to use the method claimed because no guidance is provided in the specification as to what agents will be useful for modulating signal transduction by binding the TNF-R or by binding to an effector protein that interacts with the TNF-R."

It is difficult to review the examiner's rejection as expressed in the Answer because the examiner has not addressed the requirements of any individual claim on appeal. While certain of the examiner's statements may be correlated to the requirements of some of the claims on appeal, and in responding to appellants' arguments presented in their Appeal Brief, the examiner has further elaborated her position, we do not have a precise, coherent statement why any single claim on appeal is unpatentable.

Turning first to the screening claims, we find that this aspect of the rejection can be easily decided. As seen from representative claim 37, the claimed method does not

require that molecules which interact with TNF-R to modulate signal transduction by the TNF-R be actually identified. The examiner argues at page 11 of the Answer that step c) of claim 37 was "not an optional step." However, the examiner has lost sight of the fact that step b) of claim 37 only requires a screening step to identify any molecules which bind to the target peptide. Step c) only requires further screening if any molecules are identified in step b). It may be that the material screened in screening step b) of claim 37 will not contain the specified molecules which bind to the target peptide. If so, then step c) would not be performed. That situation does not mean that claim 37 as whole is non-enabled. The examiner has not explained why the claimed screening methods would not identify the defined molecules if they are present in the material being screened.

By way of analogy, let us consider a claim directed to separating iron scrap from a waste stream by use of magnets. The fact that the waste streams processed according to that method may never contain iron scrap does not mean that the method is non-enabled.

The use claims stand on another foot in that they presuppose the screening procedure has successfully identified molecules which bind according to the claims on appeal. As we understand the examiner's position it is premised in large part upon the fact that the specification of this application does not describe a specific molecule which possesses the binding requirements of the claims on appeal. However, the lack of description of a single specific molecule does not in and of itself mean that the claims

are non-enabled. Rather, the specification need only teach one skilled in the art how to practice the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In considering the issue of undue experimentation in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), the court stated:

> In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d. 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made, based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:
>
> > The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.
>
> Ex parte Jackson, 217 USPQ 804, 807 (1982).

To the extent the examiner is concerned that the claims may contain so-called "inoperative" embodiments, the court discussed this concern in Atlas Powder Co. v. E.I.

du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984), stating:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude . . . possible inoperative substances . . . . In re Dinh-Nguyen, 492 F.2d 856, 859-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). Accord, In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); In re Anderson, 471 F.2d 1237, 1242, 176 USPQ 331, 334-35 (CCPA 1971). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

Absent a fact-based explanation from the examiner why the experimentation required to practice the methods set forth in the use claims on appeal would be undue rather than routine, we conclude that the examiner has not established a prima facie case of lack of enablement.

The examiner's rejection is reversed.

Other Issues

1. p75-TNF-R.

As explained above, the present invention involves two distinct tumor necrosis factor receptors, i.e., p55–TNF-R and p75-TNF-R. The vast majority of the disclosure in this application is directed to the p55 receptor. The most illuminating discussion of the p75 receptor in the specification appears at page 29 where appellants state:

> Although reference is made throughout to the p55-TNF-R, it is evident from what is known of the p75-TNF-R, that it functions similarly.

> Therefore the present invention encompasses modulation of the signal transduction and/or cleavage in both known TNF receptors.

Some of the claims on appeal contain an embodiment directed to the p75-TNF-R. For example, claim 34 first references a molecule which binds to the portion of TNF-R which includes certain amino acids of human p55-TNF-R or "the corresponding amino acids of the human p75-TNF-R." It does not appear from the record that the examiner has paid attention to this alternative embodiment.

Upon return of the application, the examiner should review all of the claims pending and ensure that the subject matter of each claim has been fully examined. For example, the examiner should pay special attention to that aspect of the claimed subject matter directed to p75-TNF-R in terms of claim definiteness and enablement. It may not be clear from claims, such as claim 34, which amino acids of the p75-TNF-R correspond to the p55-TNF-R amino acids recited in that claim in that it is not clear what appellants mean by use of the word "correspond." Correspond in identity? Location in the protein? Assuming one skilled in the art would understand which amino acids "correspond" between the two receptors, the question becomes would one be able to practice the claimed invention in regard to the p75-TNF-R embodiment without undue experimentation? In considering this issue, the examiner should take into account the legal standards set forth above. If the examiner decides an enablement question does arise in regard to this aspect to the claimed invention or any other aspect of the claims on appeal, we urge the examiner to review the court's opinion in Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999) since the court provided a model of a fact-based analysis of an enablement issue using the so-called

Wands factors. See In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In the future, it would be helpful to the record in patent applications if the examiner would consider enablement issues in the context of the Wands factors and make of record a fact-based analysis of the relevant factors.

The decision of the examiner is reversed.

REVERSED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

) BOARD OF PATENT
) APPEALS AND
) INTERFERENCES

Appeal No. 1999-0197
Application 08/054,970

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